A166.E1556
JACC Maarch 9, 2010
Volume 55, issue 10A

VASCULAR DISEASE

SUBENDOTHELIAL MATRIX COMPOSITION INFLUENCES IFN-GAMMA INDUCED MHCII-EXPRESSION BY ENDOTHELIAL CELLS

ACC Poster Contributions
Georgia World Congress Center, Hall B5
Monday, March 15, 2010, 9:30 a.m.-10:30 a.m.

Session Title: Vascular Biology/Atherosclerosis/Basic Science
Abstract Category: Vascular Biology/Atherosclerosis/Thrombosis/Endothelium
Presentation Number: 1166-351

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Background: Cell matrix interactions are critical to function. Embedding endothelial cells within physiologic 3D matrices (3D-EC) retains biosecretory function and limits endothelial immunogenicity.

Cardiovascular risk factors such as hyperglycemia induce alterations in matrix composition and EC functionality. We examined how glucose levels dictate interferon (IFN)γ induced upregulation of MHC II molecules with respect to the subendothelial matrix.

Methods: TC-EC and 3D-EC were grown to confluence in 0-50 mM glucose with or without 1000 U/ml IFNγ. Intracellular signaling pathways and MHC II expression were analyzed via real-time PCR, Western Blot, and flow cytometry.

Results: In absence of glucose IFNγ-induced phosphorylation of JAK- and STAT-proteins was attenuated 3.5-fold ($p<0.001$) in 3D-EC compared to TC-EC. This was mirrored by reduced HLA-DR expression in 3D-EC (real-time PCR: 0.3±0.1 vs. 0.1±0.1 relative units, $p<0.005$, flow cytometry: 68±4 vs. 37±5%, $p<0.001$). Suppressor of cytokine signaling protein (SOCS)-1 and -3 expression were 2.5-fold higher in naïve 3D-EC than in TC-EC ($p<0.002$). Matrix-embedding significantly amplified upregulation of SOCS by IFNγ ($p<0.005$).

Low and high glucose medium significantly upregulated IFNγ-dependent phosphorylation of JAK-1/2, STAT-1, and HLA-DR expression (25 mM: 0.7±0.2, 50 mM: 0.9±0.2 relative units, $p<0.0001$ vs. no glucose) in TC-EC. Glucose had no effect on increased SOCS-1 and -3 expression in 3D-EC. Thus phosphorylation of JAK- and STAT-proteins as well as HLA-DR expression (0.2±0.1 relative units) were significantly lower in 3D-EC than in TC-EC in low and high glucose ($p<0.0001$).

Conclusions: Hyperglycemia amplifies IFNγ dependent signaling in TC-EC. Increased SOCS expression in 3D-EC associates with a higher threshold at which IFNγ induces MHC II expression even in states of hyperglycemia. Matrix-embedding presents EC with the near-physiological state of substrate adherence and confluence. Our results indicate that intact cell-matrix contact may shield EC from immune recognition and atherosclerotic risk factors like hyperglycemia.